IMMUNE DESIGN

Harnessing the Immune System to Fight Cancer
This presentation contains forward-looking statements with respect to, among other things, our business, financial condition, strategy and prospects, and has been prepared solely for informational purposes. All statements, other than statements of historical fact, regarding our strategy, potential future products, prospects, plans, opportunities and objectives constitute “forward-looking statements.” These statements are not guarantees of future performance and involve a number of unknown risks, assumptions, uncertainties and factors that are beyond our control. Given these risks, assumptions and uncertainties, you should not place undue reliance on these forward-looking statements.

Important factors that could cause actual results to differ materially from those indicated by such forward-looking statements include, among others, our history of net losses and expected net losses for the foreseeable future, that we have no product candidates approved for commercialization and may never achieve profitability, that we will require additional capital to finance our operations, that we may not be able to successfully develop, obtain regulatory approval and commercialize our product candidates, all of which are novel and in early clinical development, and those other risks that will be set forth under the header “Risk Factors,” “Note Regarding Forward-Looking Statements” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our periodic reports filed with the Securities and Exchange Commission, including our Year-end Report for the period ended March 31, 2017. All statements contained in this presentation are made only as of the date of this presentation and are subject to uncertainty and changes. Except as required by law, we expressly disclaim any responsibility to update such forward-looking statements, whether as a result of new information, future events or otherwise.
Multiple Immunotherapy Approaches for Systemic Tumor Control

Developing safe products to generate and expand an anti-cancer immune response in vivo

Antigen Specific
(Cancer Vaccines)

Antigen Agnostic
(Intratumoral Vaccination)

CMB305
Next-Gen 1
Next-Gen 2

G100
Next-Gen-1

Lead Program: NY-ESO-1+
Tumors

Multiple tumor antigens +
immunostimulatory
molecules

Lead Program
In NHL
ZVex-IL-12
Novel Cancer Immunotherapies: Update

• ASCO 2017 data => Clinical Proof of Concept for two leading products from each of two distinct approaches
  
• Antigen Specific (novel cancer vaccine) platform: we believe the platform is working and has a path forward:
    - CMB305 monotherapy: considering registration path in sarcoma and other NY-ESO-1+ tumors
      ▶ Completed enrollment of randomized combo trial w/ Atezo
    - Supports development of versatile next-generation products

• Antigen Agnostic (intratumoral vaccination) approach: new data show G100 acts locally to trigger a systemic clinical benefit
  - Considering next steps as monotherapy
  - Completed enrolment of randomized combo trial w/ pembro
ANTIGEN SPECIFIC (CANCER VACCINE) PLATFORM
## Designing the Right Cancer Vaccine Platform

### Novel technologies
- Direct targeting of DCs *in vivo* w/ vector carrying RNA antigens and stimulatory molecules to prime CD8+ T cells
- Use a low inflammatory vector to minimize neutralization and induce long-term immune memory w/ safety features
- Leverage a prime-boost concept

### Rational clinical development
- Correct clinical endpoint for each technology (OS, vs. PFS or ORR)
- In addition to monotherapy, evaluate combinations with potentially complimentary agents (e.g., checkpoint inhibitor)
- Develop biomarkers to target patients more likely to benefit

### Broad commercial potential
- Off-the-shelf, low CoGS therapies are primary focus
- Clinical benefit linked to strong QoL to maximize value and reimbursement
ZVex® Platform:
First in vivo DC targeting RNA gene delivery lentiviral vector

Generating Tumor Antigen-specific T cells in vivo

- Sindbis envelope provides selective in vivo DC targeting
- Integration-deficient + replication-incompetent lentivirus backbone for safety
- Lack of prior immunity to Sindbis allows for multiple dosing

CMB305
First ZVex product delivering NYESO1 RNA to DCs in vivo

Next-gen ZVex
Delivering multiple antigens + increased immunogenicity

Odegard et al., J Immunother 2015; Tareen et al., Mol Ther 2014
Cancer Vaccines: Focus on OS and QoL vs. ORR

- Cytotoxic (e.g., chemotherapeutic) agents often produce an early ORR
- Even without ORR, immunotherapy may provide improved OS and QoL
CMB305: A Novel Prime-Boost Approach Targeting NY-ESO-1

- ZVex w/ full length NY-ESO-1 RNA
- Phase 1 completed in recurrent, locally advanced, metastatic STS, NSCLC, ovarian
- Immunogenic (CD4s/CD8s/no Ab)
- STS DCR of 63% & no mOS (20 mo)
- Safe

**Prime**

LV305

**Boost**

G305

**Prime-Boost**

CMB305

- Potent TLR4 agonist (GLA)+ full-length NY-ESO-1 protein
- Phase 1 completed in ovarian, sarcoma, melanoma, urothelial Immunogenic (CD4s/Abs)
- DCR of 67% across tumors
- Safe

- Phase 1 and 2 studies ongoing
- More immunogenic than either component
- Survival signal in STS pts that exceeds SoC
- Emerging biomarker profile to select pts
- Safe (no related Grade 3/4 AEs)

**First potential approval:**
- monotherapy in STS patients
- Ongoing randomized Ph2 (combination therapy with atezolizumab):
  - provides second potential path

**Beyond STS:**
- Leverage immune biomarkers to select patients in any NY-ESO-1 tumor (lung, breast, ovarian, bladder, etc.)
- Potential combination with other CPIs, ACT
CMB305: Using Both Arms of Immune System

ZVex Vector RNA Prime (LV305)

TR4+Protein Boost (G305)

Day: 0 7 14 21 28 35 42 49 56 63 70 77 84 365

LV305  LV305  G305  LV305  G305  LV305  G305  G305 q 8 wks
CMB305 Monotherapy in STS: mOS Not Yet Reached

25 STS pts: 14 synovial, 9 MRCL, 2 spindle
- recurrent locally advanced, relapsed and/or metastatic with limited tumor burden (<10 cm)
- 92% metastatic, 92% prior chemotherapy (52% ≥2 prior lines)
- 56% disease progression at study start
- NY-ESO-1+ by IHC
- Median duration of observation: 11.4mo

STS patients n=25

<table>
<thead>
<tr>
<th>Study</th>
<th>OS</th>
<th>Study</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td>Pazopanib¹</td>
<td>12.5 months</td>
<td>METASARC⁴</td>
<td>11.7 months</td>
</tr>
<tr>
<td>Eribulin²</td>
<td>13.5 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trabectedin³</td>
<td>12.4 months</td>
<td></td>
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</tbody>
</table>

CMB305 Monotherapy Disease Control in STS patients

- STS patients with disease progression at entry experienced durable tumor growth arrest

<table>
<thead>
<tr>
<th>STS Patients n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, pt (%)</td>
</tr>
<tr>
<td>SD, pt (%)</td>
</tr>
<tr>
<td>DCR, pt (%)</td>
</tr>
<tr>
<td>Median PFS, mos</td>
</tr>
<tr>
<td>95% CI</td>
</tr>
<tr>
<td>6 mos PFS Rate, %</td>
</tr>
</tbody>
</table>

March 31, 2017 data cut
Immunity was assessed by testing positive by NY-ESO-1 antibody ELISA or T cell ELISpot or presence of NY-ESO-1 specific pTCR.
LV305 & CMB305 Monotherapy: Induction of Immune Response is Associated with Better Survival

*All patients treated with LV305 or CMB305 (ID/IM and SQ dosing) and who had biomarker samples were analyzed (n=64)
50/64 pts (78%) of patients had an induced anti-NY-ESO-1 immune response on LV305 or CMB305 therapy (assessed by one of the antibody or T cell assays)

March 31, 2017 data cut
Biomarkers Enable CMB305 as Potential Therapy in any NY-ESO-1+ Tumor

<table>
<thead>
<tr>
<th>Tumor Type (Incidence)</th>
<th>NY-ESO-1+</th>
<th>Addressable Market (new cases/year in US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial Sarcoma 570</td>
<td>95%</td>
<td>Current Development 1,625</td>
</tr>
<tr>
<td>MRCL 1,230</td>
<td>80%</td>
<td>Total ~48,000 to ~102,000</td>
</tr>
<tr>
<td>NSCLC 222,500</td>
<td>11-25%</td>
<td>Potential ~46,000 to ~100,000</td>
</tr>
<tr>
<td>Melanoma 87,110</td>
<td>24-45%</td>
<td></td>
</tr>
<tr>
<td>Ovarian 22,440</td>
<td>14-43%</td>
<td></td>
</tr>
</tbody>
</table>

- **Other NY-ESO-1(+) tumors:** Bladder (TCC), Breast, Colorectal, Gastric, HCC, Head & Neck, Multiple Myeloma, Esophageal, Prostate, Thyroid, Uterine, Cholangiocarcinoma, Endometrial, Neutoblastoma, NHL (DLCL), Renal, other Sarcomas

https://seer.cancer.gov/statfacts/; [http://www.cta.incc.br/index.php](http://www.cta.incc.br/index.php); Jungbluth et al., 2001b; Jungbluth et al., 2001a; Nicholaou et al., 2006; Hudolin et al., 2013; Gjerstorff et al., 2013; Demirovic et al., 2010
Next-gen ZVex: Multigenome Vector Mimics Viral Evolution

- Expression of **multiple antigens** and immune enhancers (e.g., MAGE-A1, A3, A4, & IL-12)
- **No antigen suppression**/competition within DCs
- Potential for increased immunogenicity via vector improvements & payload

### Conserved Antigens
- Mage A1
- Mesothelin
- PSA
- WT1
- SSX2
- MUC1
- PSMA
- NY-ESO-1
- Other

- Any “conserved” or viral antigens could be combined
- Multi-antigen product designation planned for Ph1 in 2018

### Neo-antigens
- Bypasses need for imperfect informatics algorithms trying to select the “right” neo-epitopes
- Pre-clinical
ANTIGEN AGNOSTIC
(INTRATUMORAL IMMUNIZATION)
Designing the Right Intratumoral Immunization

**Novel technology**
- Design a safe innate immune activator: TLR4 agonist (G100) activates multiple signaling pathways (i.e., modeling “detoxified LPS”)
- Activate peri-tumor DCs to boost pre-existing T/NK cells, facilitate *de novo* antigen presentation, and act at the level of tumor cell (APC/B cells)
- Induce systemic anti-tumor immune response from a single site, local injection

**Rational clinical development**
- Design with the correct endpoints: evidence of overall responses (including abscopal) that are durable
- In addition to monotherapy, develop in combo w/ potentially complimentary agents (e.g., checkpoint inhibitor, other)
- Consider biomarkers to define patients more likely to respond

**Broad commercial potential**
- Develop an off-the-shelf, low CoGS therapy
- Clinical benefit linked to strong QoL to maximize value and reimbursement
G100: Potent Activator of DCs for *in situ* Immunization

**Designed to activate the immune system in the tumor microenvironment**

**TLR4 agonists:**
Activation of (dual) TLR4 signaling and non-canonical inflammasome

**Activation of Innate Immune System via-DCs**

**Activation & Expansion of a Th1 Adaptive Immune System**

**GLA**
(Glucopyranosyl lipid A)

**G100**
GLA formulated in a stable emulsion (SE)

**Ph1s in MCC, sarcoma**
**Ph2 in NHL**

**Safety database of >1500 individuals**
Developing a Potent Intratumoral Immunization

**G100**
- Potent TLR4 agonist
- Synthetic, highly scalable
- Immunogenic (CD4s/Abs)

**Beyond FL:**
- Potential therapy in any accessible tumor
- Potential combination with other CPIs, ACT, oncolytic viruses

**Merkel cell carcinoma**
- Phase 1 completed
- 50% ORR per protocol
- Induced multiple anti-cancer changes to TME
- Safe

**First potential approval(s):**
- Monotherapy (+XRT) or combination therapy (+XRT, CPI) in follicular non-Hodgkin’s lymphoma (FL)
- Ongoing randomized Ph2 with pembrolizumab
- Phase 1 monotherapy DE completed (n=9)
- 44% ORR
- Abscopal lesion reduction
- Induced multiple positive changes to TME
- Safe

*After EOS visit, patients enter long-term follow-up with restaging q8 wks*
G142 Monotherapy Dose Escalation Objective Response Rate in FL Pts

<table>
<thead>
<tr>
<th>Group</th>
<th>N=</th>
<th>PR/PRu</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>9</td>
<td>4 (44.4%)</td>
<td>5 (55.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Part 1: 5µg</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Part 1: 10µg</td>
<td>3</td>
<td>1/1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Part 2: Large Tumor 20µg</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Tumor response is determined by bi-dimensional measurements and change in sum of product of tumor diameters (SPD) using IrRC Criteria based on bi-dimensional WHO criteria (Wolchok ClinCanRes 2009).
G142 Monotherapy Dose Escalation: Durable Abscopal Shrinkage in FL Pts

% Abscopal Shrinkage

Duration of Abscopal Shrinkage

* treatment Naïve

* 5 µg G100
* 10 µg G100
* 20 µg G100
Intratumoral ZVex/IL12: Highly Efficacious in Solid Tumor Models

A) B16 Melanoma Model, Footpad

B) B16 Melanoma Model, Flank

C) CT26 Colon Carcinoma Model

D) Neuroglioblastoma Model, Flank

Therapeutic effect of ZVex/IL12 is mediated by CD8, CD4 & NK cells
Intratumoral Vaccination Has Broad Potential

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Incidence (new cases/year in US)</th>
<th>Current Development</th>
<th>Total Addressable (development + near-term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>fNHL</td>
<td>~14,400¹,²</td>
<td>Watch &amp; Wait 6,700 to 10,000⁵ (Treated Prevalence)</td>
<td>~147,980 to ~151,280</td>
</tr>
<tr>
<td>Merkel Cell Carcinoma</td>
<td>~1,600³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous T-Cell Lymphoma</td>
<td>~2,900¹,⁴</td>
<td>Potential (near term)</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>87,110¹</td>
<td>~141,280</td>
<td></td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>49,670¹</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Other tumors targeted intratumorally in current clinical development: Breast, Pancreatic, Soft Tissue Sarcoma, HCC, Liver mets, Squamous Cell Carcinoma, Gastric, Renal Cell Carcinoma, B-cell lymphoma, Colorectal

⁴. [https://www.lls.org/sites/default/files/file_assets/cutaneoustcelllymphoma.pdf](https://www.lls.org/sites/default/files/file_assets/cutaneoustcelllymphoma.pdf); CTCL ~4% of NHL.
TEAM, PIPELINE AND NEWSFLOW
## Team: Experienced and Proven Leadership

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Prior Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carlos Paya, MD, PhD</strong></td>
<td>President and Chief Executive Officer</td>
<td>élan</td>
</tr>
<tr>
<td><strong>Stephen R. Brady, JD, LLM</strong></td>
<td>Executive Vice President, Strategy &amp; Finance</td>
<td>Lilly Proteolix</td>
</tr>
<tr>
<td><strong>Wayne Gombotz, PhD</strong></td>
<td>Chief Development Officer</td>
<td>Omeros Immunex</td>
</tr>
<tr>
<td><strong>Jan H. ter Meulen, MD, PhD, DTM&amp;H</strong></td>
<td>Chief Scientific Officer</td>
<td>LI L X C O M E R S R E S E A R C H</td>
</tr>
<tr>
<td><strong>Sergey Yurasov, MD, PhD</strong></td>
<td>Senior Vice President, Chief Medical Officer</td>
<td>Clovis Oncology</td>
</tr>
<tr>
<td><strong>Frank J. Hsu, MD</strong></td>
<td>Vice President, Head of Oncology</td>
<td>Genzyme</td>
</tr>
<tr>
<td><strong>Christopher Whitmore, CPA</strong></td>
<td>Vice President, Finance &amp; Administration</td>
<td>AcelRx Pharmaceuticals, Inc.</td>
</tr>
</tbody>
</table>
Team: Exceptional Board and Advisors

**Board of Directors**

- Ed Penhoet, PhD° (Chair)
- David Baltimore, PhD,* §° Independent
- Franklin M. Berger, Independent
- Carlos Paya, MD, PhD, IMDZ

- William R. Ringo, Independent
- Peter Svennilson, TCG
- Susan Kelley, MD, Independent
- Lewis W. Coleman, Independent

**Scientific Advisors (SAB)**

- Rafi Ahmed PhD,§ Emory (Chair)
- David Baltimore, PhD,* §° Caltech
- Larry Corey, MD,° FHCRC
- Phil Greenberg, MD, FHCRC

- Carl June, MD,° U of Penn
- Ron Levy, MD,§° Stanford
- Steven Reed, PhD, IDRI
- Inder Verma, PhD,§° Salk Institute

**Clinical Advisors (CAB)**

- Mario Sznol, MD, Yale
- Jedd Wolchok, MD, PhD, MSKCC
- Jeff Weber, MD, PhD, Moffitt
- F. Stephen Hodi, MD, Dana Farber

- Patrick Hwu, MD, MD Anderson
- Nina Bhardwaj, MD, PhD,° Mt. Sinai
- Kristen Hege, MD, Celgene
- Robert Maki, MD, PhD
# Diversified Immunotherapy Pipeline

<table>
<thead>
<tr>
<th>APPROACH</th>
<th>PROGRAM</th>
<th>INDICATIONS</th>
<th>Precl</th>
<th>Phase 1/1b</th>
<th>Phase 2</th>
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<tbody>
<tr>
<td>Antigen Specific</td>
<td>IMDZ-CMB305</td>
<td>Multiple Solid Tumors</td>
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<tr>
<td></td>
<td>IMDZ-LA51</td>
<td>Multiple Conserved Antigens</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>CMB305+G100</td>
<td>Soft Tissue Sarcoma</td>
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<td></td>
<td></td>
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<tr>
<td>Antigen Agnostic</td>
<td>IMDZ-G100</td>
<td>Follicular NHL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>IL-12</td>
<td>TBD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **IMDZ-CMB305** - Soft Tissue Sarcoma
- **IMDZ-LA51** - Multiple Conserved Antigens
- **CMB305+G100** - Soft Tissue Sarcoma
- **IMDZ-G100** - Follicular NHL
- **IL-12** - TBD

**Approach Details:**
- **Antigen Specific**
  - Monotherapy
  - Monotherapy
  - + atezoluzimab
  - Reg trial - potential start 2018
- **Antigen Agnostic**
  - + XRT +/- pembrolizumab
  - Monotherapy
  - Monotherapy (high dose)
Upcoming Newsflow and Financial Highlights

- IMDZ-CMB305: Soft Tissue Sarcoma
- IMDZ-LA51: Multiple Conserved Antigens
- IMDZ-G100: Follicular NHL

2H'17
- Monotherapy Expected FDA Feedback
- Combo+atezo Early rP2 data (n=36)

1H'18
- Monotherapy Potential Pivotal Start

2H’18
- Combo+atezo 18mo Survival read
- Monotherapy Potential Trial Start
- Combo+pembro Full rP2 data (=24)
- Potential Pivotal Start

*All timing is estimated and represents the intent of the company at the time disclosed

- Cash as of March 31, 2017: $90 million
- Expected cash runway: 2H 2018
- Total shares outstanding: 25.4 million
ADDITIONAL INFORMATION
LV305 STS: Impact on Pt. Survival Builds Over Time

Target lesions in patients with PD at baseline: delayed partial response in an STS patient with immune response

### Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Synovial</th>
<th>MRCL</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Pts who died</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Median, mos</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>95% CI</td>
<td>7.0 - NE</td>
<td>5.2 - NE</td>
</tr>
<tr>
<td>12 mos OS Rate</td>
<td>84%</td>
<td>83%</td>
</tr>
<tr>
<td>18 mos OS Rate</td>
<td>76%</td>
<td>67%</td>
</tr>
</tbody>
</table>

March 31, 2017 data cut

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<table>
<thead>
<tr>
<th>Study</th>
<th>OS</th>
<th>Study</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib¹</td>
<td>12.5 months</td>
<td>METASARC⁴</td>
<td>11.7 months</td>
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<td></td>
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</tr>
<tr>
<td>Trabectedin³</td>
<td>12.4 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ZVex Induces Only Low Neutralizing Ab Titers

Sera from day 77, one week after last ZVex dose (n=4)
CMB305 Monotherapy Anti-NY-ESO-1 Baseline and CMB305 Induced Immunity

- CMB305 generates strong and broad anti-NY-ESO-1 immune response (IR):
  - Stronger T cell response (ELISPOT), and positive at more time points
  - Antibody induction
  - 32% pts with induction of integrated immune response (T cells + Abs)
  - Evidence of increased antigen spreading (36% vs. 17%, n=12 pts each)

March 31, 2017 data cut

All tumor types (n=33): 24 sarcoma pts, 9 ovarian pts
Integrated IR: Antibodies, CD4 and CD8 T-cells are present post-Tx
CMB305 Monotherapy is Very Well Tolerated

Monotherapy data across multiple tumor types:

<table>
<thead>
<tr>
<th>Patients with at least one*</th>
<th>All patients (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>All TEAEs</td>
<td></td>
</tr>
<tr>
<td>TEAEs (all grades)</td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>45 (92)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>18 (37)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>11 (22)</td>
</tr>
</tbody>
</table>

| Related TEAEs             |                     |
| Grade 1-2                 | 33 (67)             |
| Grade 3                   | 3 (6.1)             |
| Grade 4                   | 0                   |
| Grade 5                   | 0                   |
| Serious TEAEs             | 2 (4)               |

Most common treatment related TEAEs: fatigue, injection site pain, influenza like illness, myalgia, injection site reaction (all self-limited)
G100 Activates Three Signaling Pathways: MyD88, TRIF and Caspase 11

Desbien A et al., Eur J Immunol, 2015

Modified from: Akira S. & Takeda K., Nat Rev Immunol, 2004

IL1, IL6, IL12, TNFα
G100 Mono- and Combination Therapies in B16 Model

G100 Monotherapy

- Vehicle control
- GLA/SE i.m.
- GLA/SE i.t.

G100 + Check Point Inhibitors

- GLA - SE only
- Irradiation + GLA - SE
- GLA + LTF2
- anti-PDL1
- GLA + anti-PDL1
- anti-PD1
- GLA + anti-PD1
- anti-CTLA4 (9H10)
- GLA + anti-CTLA4 (9H10)
- anti-CTLA4 (9D9)
- GLA + anti-CTLA4 (9D9)

G100 + anti-CD40

- SE
- GLA + 2A3
- Anti-CD40 + SE

G100 + γ Irradiation (1x 10Gy)

- PBS
- GLA - SE only
- Irradiation
- Irradiation + GLA - SE
G100 Pilot Study: clinical benefit and induced TME changes in Merkel cell carcinoma (MCC) patients

- G100 monotherapy (+XRT) resulted in a 50% ORR in MCC pts (n=10)

- G100 induced multiple changes in the TME
  - Th1-type inflammatory changes (“cold” to “hot”): increased inflammation and influx of T- and other immune cells into TME
  - G100 gene signature in all patients: Pro-inflammatory cytokines/chemokines: FOS, LTF, IL17B, EGR1, CCL23, IL17A, CLEC4C, IL26, and CCL28
  - Gene signature in clinical responders:
    - Macrophage and T-cell chemotaxis (SPP1)
    - Adhesion of macrophages (MSR1)
    - Activation of T-cells and monocytes (ALSCAM)
    - Activation of dendritic cells (TREM2)
    - Antigen processing (CTSL)
    - Neutrophil chemotaxis (IL8)

- G100 has the potential for lowering the “Cancer Immunity Set Point”
### G100 Monotherapy Abscopal Effect: Changes in TME

![Pre-G100](image1)

![Post-G100](image2)

**CD8 green; PD-1 magenta; PD-L1 red**

<table>
<thead>
<tr>
<th>Population</th>
<th>Change in Frequency</th>
<th>Change in Cell Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD1+</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>CD68+</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>CD4+</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>CD20+</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>CD8+</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>PDL1+</td>
<td>3.1</td>
<td>2.5</td>
</tr>
</tbody>
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<tr>
<th>Population</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Child population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD8+ PD1+</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>CD8+ PD1+ PDL1+</td>
<td>5.5</td>
<td>4.4</td>
</tr>
<tr>
<td>CD4+ PD1+</td>
<td>3.3</td>
<td>2.6</td>
</tr>
<tr>
<td>CD4+ PD1+ PDL1+</td>
<td>5.0</td>
<td>4.0</td>
</tr>
<tr>
<td>PDL1+ only</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>PD1+ only</td>
<td>1.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>
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Tumor infiltration by activated CD8 and CD4 T

PD-L1 expression is primarily in the CD4 and CD8 T cell

Cyan blue- CD20; Red - PD-L1; Green - CD8; Yellow - CD68; Orange- CD4
**ZVex+G100 (“Prime-Pull”) Eliminates Large B16 Tumors and Generates Long-Term Protection Via Epitope Spreading**

Methods

C57BL/6J mice (10 females/group) were inoculated with $1 \times 10^5$ B16/OVA cells, flank SC. When tumors became palpable (Day 7), mice were immunized with $1 \times 10^{10}$ vector genomes of ZVex/OVA, SC, and/or 5 mg G100. Tumor growth was monitored 2-3 times per week. Mice were sacrificed as tumor area exceeded 200 mm$^2$. Error bars represent Mean ± SEM. * $p < 0.05$; ** $p < 0.005$; **** $p < 0.005$. 

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**1st Tumor Challenge: B16/OVA**

- **Ctrl**
- **ZVex**
- **G100**
- **ZVex + G100**

Rechallenge survivors (16/18) on Day 109.

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**B16/OVA Flank Tumor Growth**

- **Ctrl**
- **B16/OVA Rechallenge**

15/15 survivors rejected 2nd tumor (B16/OVA) challenge.

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**Percent survival**

- **Ctrl**
- **ZVex**
- **G100**
- **ZVex + G100**

9/15 survivors rejected 2nd tumor (B16) challenge.